

Antimicrobials in Animal Husbandry

Materials for the December 4-5, 2008 Meeting of the California Environmental Contaminant Biomonitoring Program (CECBP) Scientific Guidance Panel (SGP)

Agenda Item: "Consideration of Potential Designated Chemicals"

Exposure or potential exposure to the public or specific subgroups:

There are 12 classes of antimicrobials registered for use in livestock and poultry production to treat and prevent infections and to promote growth. Since there is no required reporting of the use of antimicrobial agents in food animals, use estimates vary widely. The Institute of Medicine and National Research Council estimate that approximately 40% of total antimicrobials produced are used as feed additives in animals (IOM and NRC 1980). The Union of Concerned Scientists (Mellon et al. 2001) estimates that 70% of total U.S. antimicrobial use is for non-therapeutic purposes in livestock. Table 1 lists the antimicrobials approved for use in American cattle, sheep, swine, and poultry production. Some of the antimicrobials are used exclusively in animals. More than half of the antibiotics used for non-therapeutic purposes in animals are also used to treat human disease (Mellon et al. 2001).

The amounts of antimicrobials applied to feed range from 2.5 to 125 mg/kg bodyweight, depending on the animal and on the antimicrobial (McEwen and Fedorka-Cray 2002). Humans are exposed to antimicrobial residues from ingestion of contaminated animal products and from environmental exposures that originate from contaminated animal waste. The Food Safety Inspection Service of the U.S. Department of Agriculture (USDA), through the National Residue Program (NRP), conducts routine testing (both scheduled and "inspector generated") to determine if tolerances are being exceeded.¹ In 2006, of the 3,556 samples analyzed for antibiotics, 197 tested positive, of which 24 were violations. Environmental exposures may be significant; poor animal gut absorption means that as much as 90% of the parent compound may be excreted (Kumar et al. 2005, Sarmah et al. 2006). In addition, antimicrobial metabolites may be transformed in the environment back to the parent compounds after excretion (Langhammer 1989).

Known or suspected health effects:

No studies measuring antimicrobial residues in humans were found. Other than rare reports of allergic reactions (Dayan 1993), there is little literature on direct health effects specifically attributed to the presence of antimicrobial residues in humans. Based on a review of current literature, the major concern regarding the use of antimicrobials in animals is the development of drug-resistant bacteria that can be transmitted from animals to humans. Widespread concern about antimicrobial resistance tends to focus on the clinical use of antimicrobials in humans even though "the scale of clinical use and misuse is dwarfed by the magnitude of the largely unregulated use of antimicrobials in agriculture" (Silbergeld et al. 2008). Silbergeld et al. (2008) explain that "reservoirs of resistance," where resistant genes, generated by the use of antimicrobials in animal production, collect in environmental reservoirs and are transferred

¹ Scheduled testing is conducted on 230-300 animals of a production class (e.g., roaster pigs) when they present for slaughter. This sampling scheme is based on the calculation that sampling 230-300 animals for each compound assures a 90 percent and 95 percent probability, respectively, to detect residue violations if the violation rate in the population is equal to or greater than one percent (NRP 2006).

among microbial communities, must be eliminated in order to reduce the development and transmission of resistant microorganisms.

Resistant organisms are transmitted from animals to humans via consumption of contaminated meat, animal-to-human transfer, animal-to-animal transfer, and through the environment (Silbergeld et al. 2008). In ecological studies, clinical isolates resistant to a specific antimicrobial were discovered after the antimicrobial was introduced into feeding operations (Gupta et al. 2004), and fewer resistant isolates were found in humans after the use of a specific antimicrobial was banned (Klare et al. 1999). In cross-sectional studies, resistant organisms have been linked to humans, farm animals, and grocery store meats (Donabedian et al. 2006), and resistant bacteria in food products have been linked to antimicrobial use in animals (Luangtongkum et al. 2006, Price et al. 2005).

Resistant organisms are also known to travel from animals to humans via non-food sources. Clones of resistant organisms found in farm animals have been detected in people living and working on farms (Huijsdens et al. 2006), and in one experimental study, chickens were inoculated with a particular strain of *E. coli* that was later found in poultry house workers (Ojeniyi 1989). There have also been documented transfers of organisms from animals in confined animal feeding operations (CAFOs) to insects (Nichols 2005), rodents (Henzler and Opitz 1992), and birds (Cole et al. 2005).

Exposure to resistant organisms through environmental contamination from animal production is thought to be significant. Waste disposal appears to be the major source for these resistant pathogens (Silbergeld et al. 2008) as resistant organisms are present, and tend to persist, in animal waste (Hayes et al. 2004, Jensen et al. 2002). Resistant bacteria, as well as antimicrobials themselves, have also been detected in air upwind and downwind of animal feeding operations (Bull et al. 2006, Gibbs et al. 2006, Hamscher et al. 2003, Power 2004). Resistant organisms and genes have been detected in groundwater near hog farms (Anderson and Sobsey 2006, Mackie et al. 2006, Stine et al. 2007). Resistant organisms and resistance genes have been detected in soil, but it is difficult to determine if the resistance is due to the application of animal waste (Silbergeld et al. 2008). Humans are also exposed to resistant organisms in food crops that were grown in soil irrigated with water contaminated by CAFO runoff (Islam et al. 2004, Sivapalasingam et al. 2004, Tauxe 2002).

Need to assess efficacy of public health actions:

Antibiotic resistance is a large and growing public health problem. The loss of effective treatments and the increasing prevalence of multi-drug resistant bacteria can lead to increased morbidity and mortality. Monitoring of antibiotic resistance in human microflora could serve as a tool to assess the efficacy of efforts to reduce use of antibiotics in food animal production on antibiotic resistance.

Potential to biomonitor:

The focus of current scientific efforts is on tracing resistant organisms found in humans or in the environment back to animal operations (see above) and on studying the biological effects of antimicrobial residues on human intestinal microflora (Cerniglia and Kotarski 2005).

1. Testing levels of antimicrobial residues in humans:

No data were found on levels of antimicrobial residues in humans. Detection of antimicrobial residues from animal husbandry activities in humans is unlikely due to the low-doses and water solubility of compounds, leading to very low concentrations. In addition, any antimicrobial biomonitoring program would have to account for direct human use of the antibiotics of interest.

Availability of analytical methods: LC/MS/MS for chlortetracycline (metabolites: 4-epichlortetracycline, isochlortetracycline (ICTC), 4-epi-ICTC, N-demethyl-ICTC), oxytetracycline and its hydrochloride (metabolites: 4-epioxytetracycline, N-demethyloxytetracycline), tetracycline and its hydrochloride (metabolites: 4-epitetracycline, and N-demethyltetracycline). ELISA and LC/MS/MS for Penicillin G sodium salt. ELISA, HPLC, LC/MS/MS for Tylosin tartrate 1405-54-5.

Availability of adequate biospecimens: Blood.

Incremental analytical cost: The California Department of Public Health (CDPH) laboratory, while it has the equipment, would have to develop expertise and methods to analyze these compounds.

2. Bacteria and resistance testing:

One option that would better get at the question of interest (the presence of resistant organisms in humans) would be to biomonitor for microorganisms and do further testing for resistance patterns. This sort of biomonitoring would be along the lines of the National Antimicrobial Resistance Monitoring System (NARMS) for Enteric Bacteria, which was established in 1996 and is a joint program between the Centers for Disease Control and Prevention (CDC), the FDA, and the USDA. This would be more in keeping with the emphasis in the scientific literature and would meet recommendations made at the first FAO/WHO workshop on this topic, which concluded that data from surveillance of antimicrobial resistance in bacteria are essential for risk assessment and risk management (JETACAR 1999).

There are certain challenges to this sort of approach. CDPH and Department of Toxic Substances Control (DTSC) labs do not perform this type of testing and the Program would have to collaborate with University researchers in order to have these types of analyses completed in a time of limited budgets. Furthermore, without substantial upstream testing, it would not be possible to determine the source of these resistant organisms. Communication of results to participants would require that significant attention be paid to the distinction between being colonized with a resistant bacteria and having an infectious disease that requires treatment.

Availability of analytical methods: Antimicrobial resistance testing would entail assessment of antimicrobial resistance in gastrointestinal flora in stool cultures or in upper respiratory tract flora in nasal swab cultures. Urine and blood samples are normally sterile and do not contain bacteria. Therefore, these samples would not be useful for screening of the general population.

Availability of adequate biospecimens: Stool, nasal swabs

Incremental analytical cost: Testing could not be completed with current laboratory capabilities – outside researchers would need to be involved and funded.

Table 1: Selected antimicrobials registered for use in food and companion animals in the U.S. Adapted from Silbergeld et al. 2008, Miller et al. 2001, and AHI 2007.

Group/Class	Antimicrobial	Usage	Sold (weight) ²	
Ionophores	Monensin*	Cattle	11 million pounds	
	Lasalocid*			
Arsenicals	Arsenilic acid*	Poultry		
	Roxarsone*, cabarsone*			
Glycolipids	Bambermycin*	Pigs, poultry		
Pleuromutilins	Tiamulin*	Pigs		
Quinoxalines	Carbadox*	Pigs		
Tetracyclines	Tetracycline [†]	Pigs	< 9.3 million pounds	
	Chlortetracycline [†]	Cattle, pigs, poultry		
	Oxytetracycline [†]	Cattle, pigs		
Cephalosporins	Ceftiofur sodium [‡]	Cattle, swine	< 4.5 million pounds ³	
	Cephapirin [‡]	Cattle		
Macrolides	Erythromycin [¥]	Cattle		
	Oleandomycin*	Chickens, turkeys		
	Tylosin [†]	Cattle, pigs, chickens		
Lincosamides	Lincomycin [†]	Pigs		< 1.2 million pounds
Polypeptides	Bacitracin [†]	Cattle, pigs, poultry		
Streptogramins [¥]	Virginiamycin	Swine		
Sulfonamides	Sulfamethazine [†]	Cattle, pigs		
	Sulfathiazole [†]	Pigs		
Penicillins	Penicillin [†]	Poultry	< 0.3 million pounds	
Aminoglycosides	Gentamycin sulfate [†]	Chickens, turkeys, swine		
	Neomycin [†]	Cattle, swine, sheep, goats		
Elfamycin	Efrotomycin*	Pigs	Data not available	

¥: used to treat human diseases with few or no alternatives. Specifically, Virginiamycin is closely related to quinupristin-dalfopristin, a last-ditch treatment for Methicillin Resistant *Staphylococcus aureus* and Vancomycin Resistant *Enterococcus faecium* infections, both of which are potentially fatal in humans (Khan et al. 2008).

€: not used in humans, but belong to class of antimicrobials used in humans

£: used to treat human diseases, for which alternatives exist

*: not currently used to treat human diseases.

² These figures are based on a survey of members of the American Health Institute (AHI), the industry trade group for companies that make animal pharmaceuticals, and include amounts of antimicrobials sold for use in farm *and* companion animals. It is not possible to determine from the AHI figures the amounts used only in food animals, with the exception of ionophores, which are not used in companion animals. However, food animal production likely constitutes the great majority of antimicrobial use in animals.

³ This figure includes fluoroquinolones, which were banned for use in food animals by the FDA in 1997.

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